Remarks

The above Amendments and these Remarks are in reply to the Office Action mailed January 10, 2008. A Petition for Extension of Time and the appropriate fee are included herewith.

Applicants appreciate the Examiner's withdrawal of rejections of claims 1-8 under 35 U.S.C. 112, second paragraph, and rejections under 35 U.S.C. 102(b) over Barry or Slonim.

I. New Matter

The Examiner rejected Claims 1-6 and 8-17 under 35 U.S.C. 112, first paragraph for allegedly containing new matter.

Applicants have amended Claims 1-3, 5-6 and 8, and believe that the language that formed the basis of the rejections have been removed or supported.

Applicants have amended Claims 1, 3 and 8 to include specific details of the systems and methods that combine classified gene expression data and classified clinical data into a combined output. These details are fully supported in the application as filed at least in FIG. 3b and in paragraphs [0077] – [0115].

In particular, FIG. 3b shows an example of how improved accuracy of making medical decisions can be implemented. First, gene expression data (e.g., microarray data; shown on the bottom left of FIG. 3b) is collected and classified using an EFuNN process in a Predictor module layer. Classification of gene expression data produces two predicted outcomes, Class A and Class B as shown in the Class unit layer. Connection weight $\__1$ provides the relative certainty that the classified gene expression data accurately predicts the outcome Class A. Connection weight $\__2$ provides the relative certainty that the classified gene expression data accurately predicts the outcome Class B. Applicants submit that these points are clear based on FIG. 3b.

Next, clinical information (IPI) is collected and classified using a Bayesian classifier in a Predictor module layer. Classification of clinical information produces two predicted outcomes, Class A and Class B. Connection weight $(1 - \__1)$ provides the relative certainty that the classified clinical information accurately predicts outcome Class A. Connection weight $(1 - \__2)$ provides the relative certainty that the classified clinical information accurately predicts the outcome Class B. Applicants submit that these points are clear based on FIG. 3b.

Next, information from both Class unit layers is combined to produce a Combined Prediction (Class A/Class B) in the Decision layer using connection weights α and $(1 - \alpha)$. Applicants submit that these points are clear based on FIG. 3b.

Finally, as described in paragraphs [0078] – [0115], three methods are described to minimize the error in the Combined Class A/Class B prediction as claimed in Claim 2. These are an exhaustive search method

(see paragraphs [0080] – [0085]), a statistically based specialization method (see paragraphs [0093] – [0112]), and a multi-layer perceptron (see paragraphs [0113] – [0114]).

Further support for the amendments to the claims can be found in the Declaration of Dr. Nikola Kasabov attached hereto as Appendix 1 (Kasabov Declaration). In particular, referring to paragraph 18 of the Kasabov Declaration, the general method is described as "explained in paragraphs 074 till 085 and Fig. 3b." Further,

> An information scientist can implement the explanation into the following formulas:
> Class unit layer:
> Combined Class A Output: ClassA output = (C1/classA x $\beta 1$) + (C2/classA x $\beta 2$)
> Combined Class B Output: ClassB output = (C1/classB x $(1 - \beta 1)$ + (C2/classB x $(1 - \beta 2)$)
> Decision layer (optional):
> Combined output = (Combined ClassA output x α) + (Combined ClassB output x $(1 - \alpha)$,
> The final output will be between 0 and 1. If close to 0, the diagnosis is Class A if closed to 1, the final diagnosis is Class B.

Thus, Applicants respectfully submit that the amendments to the claims are fully supported and that no new matter has been introduced into the application.

II. Rejections under 35 U.S.C. §101

Claims 1-6 and 8-17 stand rejected under 35 U.S.C. §101 because these claims "are drawn to non-statutory subject matter." Office Action, page 4.

Claim 1 has been amended to include an "output device." Similarly, Claim 3 has been amended to include the step of "displaying said outcome." Applicants submit that these amendments are fully supported implicitly by the nature of the system and the methods as described throughout the application as filed. Furthermore, explicit support for the amendment can be found at least in FIG. 1, where an "Output Device" is shown in the box near the bottom, and in the further outputs to either "Screen" or "Written Report" shown at the bottom of FIG. 1. Applicants submit that both "Screen" and "Written Report" supports the step of "displaying said outcome.'

Further, Applicants respectfully submit that the systems and methods of this invention produce a "concrete, tangible and useful result" as required by State Street Bank, in that the results produced are highly relevant to medical diagnosis, prognosis and evaluation of medical treatment. Explicit support can be found at least in the specification at paragraph [0012]: "Embodiments of this invention include novel methods for **increasing the confidence of medical decision support systems**..." [Emphasis added.] Applicants submit that it is well known that increasing the confidence of medical decisions has practical utility.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §101 be withdrawn.

III. Rejections under 35 U.S.C. §103

Claims 1-6 and 8-17 stand rejected under 35 U.S.C. §103(a) as obvious over the combination of Downs and Ben-Dor. Claims 1-3, 5-6, 8-10 and 13-15 stand rejected as obvious over the combination of Bagne and Slonim.

Non-obviousness and obviousness are analyzed according to the Supreme Court in *KSR v. Teleflex*, which relied upon the well-known factors from *Graham v. John Deere* (the "Graham factors"). Under the Graham factors, the following are considered:

1. The state of the art at the time of the invention;
2. The differences between the art and the invention;
3. The level of ordinary skill in the art; and
4. Objective indicia of non-obviousness.

1. State of the Art

The Examiner's rejection of the claims is based on two combinations of references: (1) Downs and Ben-Dor, and (2) Bagne and Slonim. As will be explained herein, the state of the art is defined by what is disclosed or taught, and by what is not disclosed nor taught.

A. Downs

According to the Examiner,

> Downs teaches a method and system using an adaptive resonance theory based on neural network modes (ARTMAP), which is broadly interpreted as an evolving fuzzy neural network. ... In particular, Downs shows a fuzzy ARTMAP voting strategy outcome [...] comprising a number of networks trained on different orderings of the training data; during testing, each individual network makes its prediction for a test item in the normal way; the number of predictions made for each category is then totaled and **the one with the highest score (or the most votes') is the final predicted category**." Office Action, pages 6 bridging to 7; emphasis added.

> Downs shows the use of clinical and electrocardiographic data considered to be useful for patient prognosis [Section 3.1], as well as the use of tissue samples for predicting breast cancer in patients [Section 4.1, p.411). ... Downs shows their system can make use of **the most highly predictive data** [...] first, and then request additional information on physical signs, associated symptoms, risk factors, clinical history etc (i.e. clinical

information) as required, **until a confident prediction could be made.** Office Action, page 7; [Emphasis added.]

The Examiner admitted "Downs does not teach the use of gene expression data. ..." Office Action, page 7.

Applicants respectfully submit that even if Down's systems and/or methods could perform as the Examiner stated, that Downs' systems and/or methods does not describe any method for increasing the reliability of making a prediction **greater than** the "most highly predictive data" or to define any criteria by which a "**confident prediction**" could be made. Rather, Downs merely uses the "highest score" as the "final predicted category."

B. Ben-Dor

According to the Examiner, Ben-Dor teaches:

> the use of gene expression data in the development of efficient cancer diagnosis and rule-based classification systems {Abstract]. Ben-Dor show a supervised procedure that can be applied to any parameter independent clustering method ... and direct methods for determining a decision surface that are related to artificial neural network applications "section 2.3, p.56]. ... One of ordinary skill in the art would have been motivated to combine the above teachings because since gene expression data provide improved insight into cancer related processes as shown by Ben-Dor [Abstract]. Office Action, page 7 bridging to page 8.

Applicants agree that gene expression data provides insight into cancer related processes. Applicants also agree that Ben-Dor teaches supervised procedures for training neural networks.

Even if Ben-Dor teaches procedures as described by the Examiner, Ben-Dor does not teach any method or systems for increasing the reliability of making a prediction. In particular, Applicants submit that Ben-Dor does not teach any quantitative methods for improving accuracy of any prediction by combining gene expression data and clinical information together to provide a "Combined Class A/Class B Output" as claimed.

Thus, the fact that Ben-Dor teaches use of gene expression information does not make up for the lack of teaching of any method for improving the accuracy of a medical decision support system as claimed. Further, because neither Downs nor Ben-Dor teach any such system or method, the combination of Downs and Ben-Dor together cannot teach any system or method for improving the accuracy of a medical decision support system as claimed.

C. Bagne

According to the Examiner, Bagne teaches:

> an improved method and system of empirical induction involving longitudinal associations used to evaluate treatments and make predictions. In particular, Bagne presents a computational method of empirical induction (MQALA) that provides high quality predictions about associations between data sets based on generalized conclusions [See Col. 64] and accounts for all characteristics of patients [Col. 68, lines 30-45]. The method of Bagne uses measured data, applies Boolean features to data to form associations (i.e., first predictions), and computes a longitudinal association score (LAS) for each selected combination of independent events with and dependent events [Ref. Claim1]. ... Bagne shows the use of discriminative analysis to identify potential predictors. ... and shows discriminative programs (i.e. modules) and memory. Office Action, page 8 bridging to page 9.

Applicants submit that as with Downs and Ben-Dor, Bagne does not teach any method for minimizing "the error of Combined Class A/Class B output" as claimed.

D. Slonim

According to the Examiner,

> Slonim et al. teach a method for classifying cancer by computational analysis of gene expression data [Abstract}, wherein treatment success Ii.e., predicted outcome) predictions are based on a correlation of classified gene expression and chemotherapy data (i.e. classified clinical information) [p.269, Col 2., paragraph1, and wherein Bayesian analysis is used for classification, prediction, adn confidence testing on all data [p.267, Section 3.3]. Office Action, page 9.

Applicants respectfully submit that Slonim does not teach any system or method for improving accuracy of predictions of a combined data set above those made for individual data sets, and thus, does not provide any system or method for minimizing "the error of Combined Class A/Class B output" as claimed. Further, the combination of Bagne and Slonim together cannot provide a system or method for minimizing "the error of Combined Class A /Class B output" as claimed.

In conclusion, the state of the art includes examples of classifiers and methods for providing predictions, but Applicants respectfully submit that none of the cited art teaches any system of method for improving the accuracy of making a prediction greater than the "best" predictor of the prior art.

2. Differences Between the Prior Art and the Invention

Relative to the state of the art described above, Applicants submit that the instant invention provides non-obvious methods and systems that actually improve the accuracy of a combined prediction compared to even the best accuracy of a prediction based on a single classifier of the prior art. For example, FIG. 3b shows a diagram of embodiments of the invention as claimed. Even if one were motivated to combine data from different types of information into a single predictor, one could not have done so as to provide a measure of reliability of the final outcome as claimed. Applicants respectfully submit that this "gap" between the prior art and the invention is so great as to be insurmountable until the Inventor's provided the needed disclosure.

The differences between the prior art and the invention are pointed out in the Kasabov Declaration. Dr. Nikola Kirilov Kasabov is an Inventor of the invention as disclosed in the instant application. Dr. Kasabov is a world-known expert in the fields of information sciences, artificial intelligence, knowwledge einineering, bioinformatics, brain-like computing an neuroinformatics and other arts (Kasabov Declaration, paragraph 2). He earned a Ph.D. Degree, and has held numerous positions in academia and industry, and is widely published (*Id.* paragraph 2). A copy of Dr. Kasabov's Curriculum Vitae accompanies his Declaration as Appendix I.

According to Dr. Kasabov, "A person of ordinary skill would apply the clinical data of a patient in the clinical data classifier and would also apply the genetic data of the same patient to the gene classifier. According to the combined teachings of Downs and Ben-Dor or Bagne and Slonim, the person of ordinary skill would identify the classifier with the higher reported accuracy, and would consider the combined date to have that degree of accuracy." Kasabov Declaration, paragraph 9.

"Specifically, a person of ordinary skill could combine, using the MAX function, a gene expression classifier by Ben-Dor for example, and a clinical data classifier of Downs, for example, to achieve an accuracy of the best of them, but neither is covered by any prior publication." Kasabov Declaration, Paragraph 11.

"Downs does not relate to our invention of integrated classifiers based on separate gene expression and clinical data or any other two or more separate data sets related to the same problem and its outcome. Downs demonstrates the use of the well-known fuzzy ARTMAP neural network model on a single clinical data set. The use of voting is to avoid one of the problems of the fuzzy ARTMAP, namely the dependence of the evolved structure on the order of the sample (example) presentation. However, this has nothing to do with our claimed methods. More specifically, the extracted rules based on Downs are only propositional and based on binary TURE/FALSE input variables and out put categories. Kasabov Declaration, paragraph 12.

In contrast with the prior art, "[t]he rules extracted using our claimed methods are fuzzy, both quantitatively and qualitatively, and can take any type of variables, including binary, categorical or continuous. Our methods can thus link the continuous variable of gene expression with clinical variables, unlike the

methods of Downs or Ben-Dor, or the combination of Downs and Ben-Dor together. Kasabov Declaration, paragraph 13.

As applied to the rejections over Bagne and Slonim, "[t]he above said is equally valid for Bagne and Slonim publications." Kasabov Declaration, paragraph 14.

An example of the improved accuracy is provided. Dr. Kasabov noted an example from the application as filed (page 14; see Kasabov Declaration, paragraph 15): "A clinical data classifier built on clinical data only had a predictive accuracy of 73.2%. A gene expression classifier, built separately on gene expression data only, had an accuracy of 78.5%. If both clinical and gene expression data is available for a new patient, the predicted outcome by the gene expression classifier will be considered only if it has a higher accuracy of outcome prediction than the accuracy based on clinical information. Thus, using the prior art methods, the patient prediction accuracy will be 78.5%." Kasabov Declaration, paragraph 16.

As stated herein above, details of computational steps implicit in FIG. 3b and in the specification as filed are described by Dr. Kasabov (see Declaration, paragraph 18). Applicants submit that given the disclosures and teachings of the instant application (specification and Figures), one of skill in the art is now in possession of all necessary and sufficient information needed to fully implement systems and methods as claimed.

In particular, Dr. Kasabov notes: "[th]e claimed methodology is illustrated with the use of three methods for calculating the introduced parameters β_1, β_2 and α:

- Method (1): exhaustive search;
- Method (2): Statistical validation;
- Method (3): Backpropagation learning algorithm for a multilayer neural network." Kasabov Declaration, paragraph 18.

"In contrast with the prior art methods, our methods (1) and (3) [see specification, paragraphs [0080] – [0092] and paragraphs [0113] – [0115], respectively] disclose how to do that through tuning three parameters, β_1, β_2 and α using the new data set. Applying our method (1) results on the same Lymphoma data in a combined classifier system with a much higher accuracy of 87.5% ! Method (2) of our invention discloses how two separate classifiers can be used on a single new patient data even if there is no other patient data set based on both clinical and gene expression data." Kasabov Declaration, paragraph 19; emphasis in original.

Thus, Applicants respectfully submit that the invention as claimed is not only novel, it is highly non-obvious. None of the prior art taught one of ordinary skill how to improve accuracy of making a prediction based on combined data from two different sources. Through the inventive methods and systems for implementing these methods, the tools available to persons of skill in the art has been dramatically improved.

3. Level of Ordinary Skill in the Art

Applicants submit that the third Graham factor, the level of ordinary skill in the art, is that skill possessed by a medical practitioner having knowledge of Downs, Ben-Dor, Bagne and Slonim. However, according to Dr. Kasabov, "[a] person of ordinary skill at the time the application was filed would not know how to modify either combination of the above references to obtain the claimed subject matter." Kasabov Declaration, paragraph 6.

Further, Dr. Kasabov stated: "[a] person of ordinary skill is a medical practitioner with access to separate gene expression and clinical information classifiers. Such available classifiers include regression formulas, Bayesian classifiers, neural networks, SVM, and other known models known in the art, or has separate data sets that allow him or her to create such separate classifiers." Kasabov Declaration, paragraph 8.

"A person of ordinary skill would apply the clinical data of a patient to the clinical data classifier and also apply the genetic data of the same patient to the gene classifier. According to the combined teachings of Downs and Ben-Dor or Bagne and Slonim, the person of ordinary skill would identify the classifier with the higher reported accuracy, and would consider the combined data to have that degree of accuracy." Kasabov Declaration, paragraph 9.

Applicants respectfully submit that the person of ordinary skill would not be able to combine data to increase the accuracy of the predicted outcome. Dr. Kasabov stated: "[i]f new data is available in which both gene expression information and clinical information is available, the person of ordinary skill would not be able to use the new data to combine with the two existing classifiers and achieve a higher accuracy than the accuracy of any of the classifiers." Kasabov Declaration, paragraph 17.

Dr. Kasabov further stated: "[t]here are no prior art methods disclosed in Downs, Ben-Dor, Bagne or Slonim nor their obvious combinations, that provide now gene expression and clinical data sets related to the same problem (but not necessarily available as a combined date vector for each person) can be integrated into a combined classifier system that produces a better accuracy than any of the single data sets used. Neither of the combinations of Bagne and Slonim, nor Downs and Ben-Dor suggest how gene and clinical variables can be integrated in a fuzzy rule (profile) of similar samples to improve the understanding in the interaction between the gene and the clinical variables." Kasabov Declaration, paragraph 20.

IV. Conclusion

Based on the amendments and arguments presented, Applicants respectfully submit that all of the amendments to the claims are fully supported by the application as filed and that no new matter has been introduced into the application. Applicants also submit that none of the combinations of references cited

render Applicants' claims obvious, and that all of the pending claims are allowable. Applicants respectfully request the Examiner to reconsider the rejections, to find the claims allowable, and to provide a Notice of Allowability.

The Examiner is respectfully requested to telephone the undersigned if he can assist in any way in expediting issuance of a patent. The Commissioner is authorized to deduct from or refund funds to Deposit Account 50-4089 for any fee related to this Reply.

Respectfully submitted,

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Appendix 1

Declaration of Nikola Kirilov Kasabov, Ph.D.

Under 37 C.F.R. 1.132